Nutrient Risk Assessment as a Tool for Providing Scientific Assessments to Regulators1–3

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Abstract

Regulatory officials world-wide are paying attention to the process for establishing the upper level of intake for nutrient substances. The rapidly expanding use of dietary supplements, fortified foods, and functional foods, coupled with increased trade in these products, has focused attention on ensuring their safety and on harmonizing standards internationally. The more traditional approaches, in which the regulators either provided no standards for upper levels of intake or developed standards based on some arbitrary multiple of the intake level known to provide an adequate amount of the nutrient, are recognized as outdated or inappropriate for the emerging issues. Preferred approaches are those that rely on the systematic scientific assessment of risk to determine the levels of intake below which no harm may occur. The scientific study of risk is playing an increased role in establishing the regulatory upper levels of “safe” nutrient intake. Risk assessment, as a component of risk analysis, offers a scientific basis for regulatory decision-making regarding the regulators’ task associated with specifying safe upper levels of intake for nutrient substances. This article describes the key components of risk assessment as they are applied within the nutrition field. Although regulatory frameworks vary from country to country and all countries retain their right to determine their own level of protection, regulatory systems operate most effectively and are more likely to converge toward harmonization if they are informed by independent, organized, and scientific reviews that are conducted systematically in a transparent manner. J. Nutr. 138: 1987S–1991S, 2008.

Introduction

The scientific study of risk is playing an increased role in establishing the regulatory upper levels of “safe” nutrient intake. The consideration of specific intake levels above which adverse effects may occur is not necessarily new to nutrients, but it is receiving more attention because of the increasing availability of dietary food supplements and specially formulated foods. Although the assessments are generally requested by regulatory agencies, the results have much broader applications and are also used by scientists, health practitioners, food producers and retailers, and consumers in myriads of research and practical applications.

Regulators in some countries are now moving toward developing regulatory policies on safe upper intake levels for nutrients and their focus now includes the use of an organized approach for scientific reviews: the use of information provided by science-based risk assessment concerning identified upper levels of intake. This approach moves away from the previously more common approaches in which the regulators either provided no standards for upper levels of intake or developed standards based on a default value that was equal to or some arbitrary multiple of the intake level known to provide an adequate amount of the nutrient.

There have been important early efforts to use the analysis of risk as a tool for managing and enhancing the usefulness of scientific input into regulatory processes, most notably the NRC’s report entitled Risk Assessment in the Federal Government: Managing the Progress (1). This study was intended to strengthen the reliability and objectivity of scientific assessment, which forms the basis for federal regulatory policies. Internationally, the Codex Alimentarius Commission, under the auspices of FAO of the United Nations and the WHO, has incorporated risk analysis into their procedural manual (2). The role of Codex is to develop food standards, guidelines, and related documents such as codes of practice that protect consumers’ health, ensure fair trade practices in food, and coordinate food standards work undertaken by international governmental and nongovernmental organizations.

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Focusing specifically on nutrients, the US National Academy of Sciences has used a risk assessment approach during the last 10 y to establish tolerable upper levels of intake for nutrients for use within the United States and Canada (3). In Europe, the Scientific Committee on Food, now subsumed by the European Food Safety Authority, has carried out similar activities for standards for the European Union (4).

An important report related to this general topic area was issued jointly by the FAO of the United Nations and the WHO in 2006 under the project leadership of the first author of this article. The report, “A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances,” (5) focused on the general principles of nutrient risk assessment. Many of the points highlighted in the present article can be found in more detail in that report. Additionally, the considerations important to adapting risk assessment for use in the nutrition field, as described below, were first presented in a background article prepared by Yetley (6) for a workshop held in 2007.

The establishment of science-based upper levels of intake is designed to protect the consumer from potentially harmful intake. An important added value is that it also protects food manufacturers who would be liable for their products if they were to cause harm. Furthermore, the results of science-based nutrient risk assessments can assist regulators in formulating a wide array of science-based policies, including food standards and food fortification practices, as well as alerting them to the need to take public health action ranging from enhanced education of consumers to restricting access to certain products. The increased consumption of dietary/food supplements, so-called functional foods, and fortified foods makes the current consideration of upper levels of nutrient intake highly relevant and an important public health issue.

**Nutrient risk assessment as a component of nutrient risk analysis**

Risk assessment is 1 of 3 overlapping activities commonly referred to jointly as risk analysis (illustrated in Fig. 1). The component known as risk management (e.g. regulatory activities) often initiates the request for a risk assessment. Risk assessment provides the science-based information that is required by risk managers/regulators who use that information, along with other data, in decisions regarding actions necessary to manage risk. An added value is the usefulness of the scientific assessment to a much broader stakeholder community, including scientists, healthcare providers, industry representatives, and consumers. To preserve the independence and the scientific objectivity of the assessment, the overall model for risk analysis emphasizes the separation of risk assessment activities from risk management activities. In this context, the role of a risk assessment is to serve as a scientific basis for and to provide transparent justification of a public health decision but not to specify the ultimate policy decisions regarding what may be specified as safe for the population. Although risk managers should and often do interact with risk assessors in determining the scope of, and problem formulation for, the assessment (5), it remains important to ensure that the risk assessment presents the state of the science but does not provide conclusions or recommendations that address policy and program decisions appropriately tasked to risk managers and other stakeholders.

Risk assessment is not a set of prescribed methods but is most akin to an organizing scheme. It defines a process for scientific review that is systematic and decision oriented. It does not require specific methods; different methodologies can be used as appropriate. As such, it works first to define and understand the problem or, in other words, to define the nature of the information that the regulator and other users want and need. The risk assessment process then moves to organizing and considering the available data, making determinations, and then finally to characterizing the risk, so as to place the outcomes in a scientific and public health context for use by regulators and risk managers.

There are 4 general steps of risk assessment (Fig. 2). The first step is to identify the hazard, which usually takes the form of some type of literature review and summary. This must be well designed to meet the purpose of the assessment and ensure that the proper data are captured, reviewed, ranked, and summarized. Based on these outcomes, the task of selecting the endpoint of interest, the so-called critical adverse effect(s), occurs along with work to describe the dose-response relationship, which may vary by age/gender groups. Expert scientific judgment comes into play here because of considerable data limitations. The outcome is the establishment of an upper level of intake or at least some indication of a level of intake below which no adverse effects are expected to occur.

But the scientific task does not stop at the identification of a specific level of intake. The risk assessment process stipulates that the scientist also considers the current exposure of the population of interest, which in the case of nutrients is the current estimated intake. With this information, risk assessors move on to a risk characterization step. They identify the percentage of the population of interest that appears to be at risk for exceeding the level of intake beyond which harm may occur. They also highlight and describe any other scientific information that may be relevant to the potential for risk. Some would argue that this is a very important and often overlooked (or perhaps underdeveloped) step in the process. It is, however, critical,
Science-based risk assessment within a regulatory context

Regulatory decisions benefit by being fully informed by sound science (7). Several basic tenets or principles are important to the regulatory context for risk assessment, especially as it relates to establishing upper levels of intake for nutrients.

First, the use of a systematic scientific approach as part of regulatory decision-making is useful, because the decisions can more readily be defended if challenged by persons outside the process. If the available science underpins the decisions, there will be a solid basis for explaining the outcome.

Second, incorporating scientific review into the regulatory process does not ensure harmony among regulators in different regions of the world, but it does result in greater opportunities for harmony in the decisions reached. If science serves as the base for regulatory decisions, differences in outcomes are more likely to be due to differences in regulatory frameworks, which can vary from country to country, rather than to differences in interpretations and use of the available science. There are a range of regulatory rules and approaches used by different countries and different levels of protection may be sought. The available science must be used in a sound and well-documented manner within this mix of frameworks, which on their own introduce understandable variability into the regulatory decisions that are made.

Third, factors other than the information provided by the scientists must be included in the development of final food policies and regulatory decision-making (7). Assuming that nutrient risk managers need to take public health actions, the risk manager uses the scientific findings in conjunction with other data and considerations, which may reflect factors ranging from legal provisions to the nature of the food supply and consumer behaviors as well as economic impact. Boxes 2–2, 2–3, 2–4 and 2–5 in the international report mentioned above (5) include detailed examples of such information and their impact on decisions. The more effective the articulation and the more relevant the results of the scientific assessment are to the public policy decisions, the more likely they will be useful and affect the policy-making arena where other nonscientific factors are also being considered. Additionally, it is important to recognize that, in this respect, the scientist as a risk assessor is not responsible for specifying the actions to be put in place by the regulators or risk managers for the purposes of meeting their standards for public health protection. The risk assessor provides the scientific information on the quantitative levels of intake that may cause harm, but the risk manager or regulator may consider that information in conjunction with other information to determine the appropriate regulatory outcome. The final regulatory level specified as safe for a population may be more conservative or liberal relative to scientific advice depending upon the ultimate goals, mitigating factors, and desired level of public health protection. The scientist’s role is to provide the scientific information about the specific levels of intake, the subsequent adverse effects at specified levels of intake, and the public health implications of these effects in the populations of interest to the risk manager. In addition, of course, the use of a science-based risk assessment approach to assist with regulatory decision-making does not diminish a country’s right to determine its own food safety standards or its own level of public health protection.

What then are the benefits of including a science-based risk assessment approach as part of regulatory activities? There are at least 5 benefits. A science-based risk assessment: 1) provides transparency; it requires considerable documentation, making the decision process accountable and clear to those outside the process; 2) is usable in the face of limited data; as an organizing process, it recognizes and integrates scientific uncertainties; 3) is flexible; it can be adjusted to deal with the diverse range of nutrients as well as the varied needs of regulators and other users; 4) maintains scientific integrity; as a documented systematic process, it keeps the scientific review component of regulatory considerations free from inappropriate influence by stakeholders; and 5) provides relevant information in a format useful and clear to regulators and other users of the assessment.

Despite these important benefits, risk assessment will not address all problems associated with making decisions about upper levels of intake. It cannot completely eliminate controversies, because data are often inadequate and uncertainties are prevalent. Further, scientific judgment can vary, because there are legitimate differences of opinion among scientists about the merits of the data and their interpretations.

Risk assessment as a set of interfaces

The overall regulatory activity associated with upper levels of intake reflects a series of interfaces (Fig. 3). First, the regulator or risk manager is responsible for formulating or specifying the problem: what science-based information is needed and for what reasons. Problem formulation often is interactive among the scientists who will do the risk assessment, the regulatory sponsors, and other stakeholders (Fig. 3, double-headed arrow).

Once problem formulation has occurred, the tasks of risk assessment begin. These are a closed set of scientific activities carried out independently and free from outside influence and include the various tasks highlighted in Figure 2 above. The final step in the assessment process is to develop the risk characterization, which is the information provided to the risk manager or regulator that links the scientific assessment to public health implications for populations of interest in response to the request made through problem formulation. It is often shown as a 1-way arrow (Fig. 3), but in reality, it may also be a 2-way arrow, because the risk manager may go back for some clarification or with additional questions or data.

This risk manager/regulator then works to integrate the science provided by the risk assessment with the other regulatory considerations that may be relevant and a legitimate component

FIGURE 3 Risk assessment interface between risk managers (regulators) and risk assessors (scientists).

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Adapting risk assessment for nutrients

The practice of risk assessment and, in turn risk analysis, is meant to be responsive to the need of the risk manager. Although the risk analysis framework was originally developed for the purposes of managing potential hazards of population (sub)groups to chemicals in foods and the environment, its use has expanded to other types of hazards (e.g. microbial pathogens in foods) and more recently to potential hazards associated with consumption of excessive intakes of nutrients and related food substances. In recent years, several expert committees have adapted risk assessment approaches to derive upper levels of intake for nutrients. These include expert panels convened by the Food and Nutrition Board of the Institute of Medicine to derive tolerable upper levels of intake as part of the process of developing the Dietary Reference Intakes for 45 nutrients and related substances (3), the Expert Group on Vitamins and Minerals convened by the government of the United Kingdom (8), and the Scientific Committee on Food convened by the European Commission (4). In 2002, a WHO expert panel proposed a risk assessment framework for analyzing an acceptable range of intake between boundaries defined by deficient and excess oral intakes of essential trace elements (9). Discussions regarding global harmonization approaches for nutrient risk assessments have been offered by Aggett (10) as well as the international report mentioned above (5).

In examining the use of risk assessment for assessing risks associated with excessive nutrient intakes, these panels identified several areas that were either unique or critical to nutrients and that differed from classical risk assessments. These included:

- Dual-curve relationship for nutrient risks. Because of their essential and documented benefit, there is risk of adverse effects associated with inadequate intakes as well as with excessively high intakes of nutrients. This differs from the single-curve relationship traditionally used for most substances for which risk assessments have been conducted (e.g. pesticides, microbial pathogens, and food additives).
- The nature of the evidence available for evaluating nutrient risk is generally incomplete and difficult to use. Most available animal and in vitro studies were not designed to evaluate the safety of high nutrient intakes, but rather were designed to evaluate beneficial effects of nutrients or to understand mechanisms of action related to classical nutrient deficiencies or to chronic disease risk reduction. These studies often failed to fully collect or report the types of information needed for risk assessment and they lacked the more complete dose-response data and wide range of potential adverse effects normally included in systematic safety studies for food additives and contaminants.
- The relatively large uncertainty factors (e.g. 100; the larger the uncertainty factor, the lower the upper level of intake) normally used to ensure public health protection given uncertainties in the evidence for nonnutrient chemicals and microbial pathogens cannot be used for nutrients, because they could result in upper level values that fall below reference values for nutrient adequacy. Thus, relatively small uncertainty factors (e.g. 0–10) are normally used in nutrient risk assessment.

Nutrients are subject to homeostatic mechanisms that involve regulation of the absorption, excretion, or tissue redistribution and retention of nutrients to maintain optimal and safe systemic supplies for essential functions and optimal health given day-to-day variability in intakes. Excessive intakes of a nutrient may compromise or overwhelm homeostatic mechanisms, resulting in an increased probability of adverse effects.

Nutrient risk assessments are generally most meaningful if provided for the life stage groups (e.g. age/gender groups, pregnant and lactating women) that are similar to the groups used for establishing reference intakes to ensure adequacy. This differs from the accumulated lifetime exposures commonly used to express the results of risk assessments for other types of hazards. For nutrients, differences in homeostatic mechanisms and requirements for growth and development among life stage groups may influence sensitivity to nutrient toxicity.

Different sources of nutrients and matrix effects of the foods consumed with the nutrient can affect their bioavailability or biopotency and therefore alter dose-response relationships.

Unlike many other potential hazards, baseline diets always provide a background level of exposure to nutrients. Although levels of intake recommended to ensure adequate diets are not considered to pose a risk for the general healthy population, the potential for excessively high intakes with the increasing availability of fortified foods and dietary supplements means that regulators or risk managers often need to consider safe ranges of intakes. Therefore, it is generally assumed that an informed decision, which represents the best estimate by qualified scientists even if based on less-than-perfect data, is preferable to giving no decision about the potential risk of excessive intakes of a given nutrient.

Implications

The development and refinement of risk assessment is an important emerging consideration in the establishment of upper levels of intake for nutrients. It offers a systematic and responsive science-based approach with considerable flexibility. It also provides the structure needed to ensure transparency and documentation, a critical factor for documenting scientific assessments used in regulatory decision-making. Nonetheless, risk assessment is relatively new to nutrient substances. Its utility will best be accomplished if time is given to the necessary task of adapting its general framework to the unique aspects of nutrients.

Other articles in this supplement include references (11–21).

Literature Cited


